REMARKS

Claims 1-4, 6-18, 20, 21, 35-38, 40-46 and 56-59 are pending and rejected. Claims 19, 34, and 47-55 are withdrawn from consideration. Applicant successfully overcame the rejection under 35 U.S.C. §102 of claims 1-4, 8, 12-13, 16 and 56-59 as allegedly anticipated by WO 01/72277 in the last Amendment and Response filed on April 13, 2009.

Rejection under 35 U.S.C. §103

Applicant submits that it was the law for about 25 years that in order to establish a proper *prima facie* case of obviousness, the patent Examiner was required to establish that there was a suggestion or motivation to modify the references or to combine the reference teachings; there had to be a reasonable expectation of success; and the references or combination of references were required to teach or suggest all of the claim limitations (*See, e.g.,* MPEP § 2142). The teachings or suggestions to make the claimed combination and the reasonable expectation of success both had to be found in the prior art and not based on applicant's disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cr. 1991)).

On April 30, 2007, the United States Supreme Court issued a unanimous ruling that changed the standards used in deciding whether an invention is obvious. In *KSR International Co. v. Teleflex, Inc.*, the Supreme Court rejected the "rigid approach" of the Court of Appeals for the Federal Circuit (CAFC) in its application of its teaching, suggestion, or motivation test (the TSM test). The TSM test has been perceived as a *requirement* that a patent is not obvious over prior-art references unless there is an explicit teaching, suggestion, or motivation to combine those references. Instead, the Court advocated an "expansive and flexible approach" to determine obviousness that focuses on the statute (35 U.S.C. § 103), as well as Supreme Court precedent interpreting that statute, including *Graham v. John Deere Co.* However, the Supreme Court did not dispense with the legal requirement that ***the references when combined much teach each and every feature of the invention as claimed.*** Applicant demonstrates in the following analysis that the Examiner has failed to set forth a proper *prima facie* case of obviousness because of the very fact that the references when combined do not teach the invention as claimed.

1. WO 91/12026 in view of Szoka, U.S. Patent 5,077,057 and optionally further in view of Sheffield *et al.*, U.S. Patent 4,937,254

The Examiner rejects claims 1-4, 6-18, 20-21, 35-38, 40-46 and 56-59 over WO 01/72277 in combination with WO 91/12026 in view of Szoka, U.S. Patent 5,077,057 and Sheffield *et al.,* U.S. Patent 4,937,254. According to the Examiner, WO 91/12026 teaches reducing surgical adhesions by coating tissue surfaces with phospholipids, including less pure phospholipids, in combination with hyaluronic acid. The Examiner says that it is obvious that this is a lamellar composition. ***The Examiner admits that WO 91/12026 does not teach the amounts of each phospholipid in the mixture*** but says that it would be obvious to optimize the relative amounts of each. Further, it would allegedly be obvious to use commercial lecithin in combination with the other phospholipids. In addition, the Examiner says the number of liposomes and administration protocol would be obvious absent evidence of unexpectedly superior results.

The Examiner says that Szoka teaches including cholesterol in liposomes to increase rigidity and encapsulating chemotherapeutic agents. Hence, it would allegedly be obvious to add cholesterol to the present compositions as well as chemotherapeutic agents. The Examiner says that Sheffield *et al.* teach inhibiting post surgical adhesion by topically administering liposomes containing phosphatidylcholine and cholesterol in combination with hyaluronic acid. According to the Examiner, it would be obvious that the preparations of WO 91/12026 would be in the form of liposomes since Sheffield *et al.* teach liposomes are formed by adding an aqueous medium to phospholipids.

(a) WO 91/12026 in view of Szoka, U.S. Patent 5,077,057

Neither WO 91/12026 nor Szoka, U.S. Patent 5,077,057 teach or suggest phospholipid compositions in the ratios of the presently claimed methods. Likewise, neither WO 91/12026

nor Szoka teaches compositions using a ratio of cholesterol according to the compositions of the presently claimed methods. Applicant submits that WO91/12026 primarily teaches using phosphatidylcholine in solution to reduce surgical adhesions. Applicant acknowledges that WO91/12026 teaches

> "less pure phospholipid may also be used, since certain impurities may act synergistically, e.g. in phosphatidylcholine the impurities tend to be phosphatidylethanolamines, phosphatidylinositols, phosphatidylserines, phosphatidylglycerides and spingomyelin."

The only guidance provided regarding individual ratios of phospholipids in the composition is that they should "preferably be kept below 0.1%." (*See*, page 6, lines 2 to 4)

In contrast to the Examiner's arguments, Applicant submits that if one of ordinary skill in the art considered providing a method with an altered composition of WO91/12026, he or she ***would be led away from the proportions presently claimed***, namely,

54% Phosphatidylcholine	
19% Spingomyelin	(190 times)
8% Phosphatidylethanolamine	(80 times)
4% phosphatidylserine, and	(48 times)
3% phosphatidylinositol	(30 times greater)

as these are significantly different from the ratios taught and suggested by WO91/12026.

In the teachings of WO91/12026, WO95/08986 is cited to show possible phospholipid compositions from soybean and egg yolk lecithin. However, ***WO91/12026 teaches ratios of these compositions that are very different from the compositions of the presently claimed methods.*** Thus, even if assuming *arguendo*, one of ordinary skill in the art was motivated to provide an alternative phospholipid vesicle for use in the treatment of surgical adhesions to that of WO91/12026 wherein the composition included each of phosphatidylcholine, spingomyelin, phosphatidylethanolamine, phosphatidylserine and phospholipidinositol, the cited documents do not suggest the selected ratios of phospholipids used in the presently claimed method.

The Examiner suggests that WO91/12026 suggests a reasonable expectation of success should phospholipids be combined to treat adhesions. Applicant submits that this expectation would not provide the person of skill in the art with motivation to try all percentage combinations of the phospolipids, given the number of possible permutations that might be used. As the ratio of phospholipids claimed is neither taught nor suggested by WO91/12026, the claimed method using the compositions indicated are patentable.

The Examiner acknowledges that WO91/12026 does not teach or suggest nor provide any motivation to include cholesterol in the phospolipid mixture. Szoka is cited to cure this deficiency. Szoka relates to the delivery of compounds having poor aqueous solubility. Szoka is not concerned with the treatment of surgical adhesions. As the Examiner indicates, Szoka teaches "liposomes incorporating cholesterol or other sterols tend to be more rigid and less permeable."

WO91/12026 does not teach or suggest nor provide any motivation to increase the rigidity of the "sheets of molecules in parallel planes." (*See*, page 3, lines 13 and 14) Szoka does not teach or suggest that liposomes comprising cholesterol might be advantageous to treat surgical adhesions. Thus, with knowledge of WO91/12026 and faced with the problem of providing an improved phospholipid composition for the treatment of surgical adhesions, one of skill in the art would not be motivated to consider the teaching of Szoka and combine this with WO91/12026. Applicant submits that the teaching of Szoka would only be considered when using hindsight with reference to the claimed invention.

However even if, assuming *arguendo*, one of skill in the art did consider the teaching of Szoka, in the absence of any further teaching he or she would consider the ratio of cholesterol used in this document. In example 2 (column 10) of Szoka, cholesterol (chol) is provided along with egg phosphatidycholine (EPC) and egg phosphatidyl glycerol (EPG) at a ratio of 7 EPG:3EPC:6Chol. In Table 2 (column 11) cholesterol is used at the same ratio as dipalmitoylphosphatidylcholine (DPPC). Thus, ***Szoka teaches compositions using a different ratio of cholesterol to the presently claimed composition***. Hence, even if WO91/12026 is combined with Szoka, the claimed invention does not result.

(b) WO91/12026 in combination with Szoka and Sheffield et al.

As discussed above, WO91/12026 does not teach or suggest compositions having ratios of phospholipids as presently claimed. As the Examiner acknowledges, ***WO91/12026 does not teach or suggest compositions including cholesterol.*** When trying to improve upon the compositions of WO 91/12026, the Examiner states that one of skill in the art would consider including cholesterol as part of the composition, as cholesterol has been included in liposome compositions in the art.

Applicant submits that Sheffield *et al.* are concerned with inhibiting post surgical adhesions and discusses topical administration of a non-steriodal anti-inflammatory drug (NSAID) in this regard. Further, Sheffield et al. teach delivery of the NSAID using a liposome, wherein the liposome can include a mixture of lipids and cholesterol. ***Sheffield et al. do not teach or suggest the advantages or disadvantages of providing particular ratios of cholesterol in the composition used to deliver the NSAID.*** In the absence of such teaching, if one of skill in the art did combine the teaching of WO91/12026 with Sheffield et al., he or she would consider the ratio of cholesterol taught by Sheffield et al. Example 13 (column 14) of Sheffield et al. teaches a ratio of phosphatidylcholine to cholesterol of 2:1 that can be suitably provided in a liposome to deliver a NSAID.

As noted above, Szoka does not teach or suggest the ratio of cholesterol of the compositions of the currently claimed methods. Therefore, Applicant submits that ***even if the teachings of WO91/12026, Szoka and Sheffield et al. are combined, the presently claimed methods featuring the compositions described do not result.*** Thus, the pending claims are patentable over the cited references.

2. Sheffield *et al.*, U.S. Patent 4,937,254 in view of WO 91/12026

The Examiner rejects claims 16-18 and 44-46 as allegedly unpatentable over Sheffield *et al.,* U.S. Patent 4,937,254 in view of WO 91/12026. The Examiner says that using the claimed phospholipids in the preparation of liposomes of Sheffield *et al.* would have been obvious since WO 91/12026 teaches that the combination of the phospholipids works synergistically. The Examiner adds that adding a chemotherapeutic agent or anti-estrogen agent would also have been obvious, particularly after cancer surgery. The Examiner maintains that starting with the teaching of Sheffield, the person of skill in the art would be motivated to include the teaching of WO91/12026 to arrive at the claimed invention.

Applicant submits that Sheffield *et al.* clearly indicate that when preparing multilamellar vesicles such as lamellar bodies (as indicated by the definition of lamellar vesicles provided by the present application at paragraph [0058]), it is preferred to use a pure or synthetic phophatidylcholine in which the fatty acid moieties in the phosphatidylcholine molecule are derived from a single fatty acid in preparing the vesicle instead of natural lecithin, which is ordinarily a mixture of compounds. In view of this teaching, Applicant submits that one of ordinary skill in the art would not be motivated to combine the teachings of WO91/12026 with the teachings of Sheffield *et al.*

The Examiner considers Sheffield *et al.* teach a method of inhibiting post surgical adhesions by the topical administration of liposomes, wherein the liposomes contain phosphatidylcholine and cholesterol. Applicant respectfully submits that Sheffield *et al.* are concerned with the effect of the active NSAID ingredient and not the liposome composition in relation to inhibition of post surgical adhesions. This is clearly taught at column 11, paragraph 2 of Sheffield as follows:

> "The NSAID active ingredient is administered to the site of surgical treatment topically. Such topical administration can be by spraying, lavage, dripping on the site by catheter administration or the like. The exact method of administration chosen has not been found to be critical, as long as an effective dose is administered over the period beginning before significant wound healing has occurred and continuing for at least the initial stages of wound healing." (emphasis added)

This is further evidenced by the results presented in Tables IX, X and XII of Sheffield *et al.* wherein more adhesions are observed when no active NSAID is provided, and little difference is observed when untreated and treated sites without an NSAID are compared. Based on the teaching of Sheffield *et al.* there is no motivation provided to one of skill in the art to combine the teaching of Sheffield *et al.* of liposomes including cholesterol with WO91/12026. ***Even if the references are combined, the claimed methods featuring the compositions described do not result, as neither Sheffield et al. nor WO91/12026 teach the ratios of phospholipids or cholesterol of the compositions of the methods claimed.***

3. Sheffield *et al.*, U.S. Patent 4,937,254 in view of WO 91/12026 further in view of Vournakis, U.S. Patent 5,624,679

The Examiner rejects claims 16-18 and 44-46 as allegedly unpatentable over Sheffield *et al.,* U.S. Patent 4,937,254 in view of WO 91/12026 further in view of Vournakis, U.S. Patent 5,624,679. The Examiner says that combining chemotherapeutic and anti-estrogens with the agents for anti-adhesion as taught by Vournakis would have been obvious.

Applicant submits that ***Vournakis does not cure the deficiencies of Sheffield et al. or WO91/12026 regarding the phospholipid and cholesterol ratios of the compositions described in the presently claimed methods.*** Thus, since claim 6 is patentable as set forth above, claims 16-18 and 44-46 are also patentable as depending therefrom.

4. WO 91/12026 in view of Szoka, U.S. Patent 5,077,057 optionally further in view of Sheffield *et al.*, U.S. Patent 4,937,254 further in view of Vournakis, U.S. Patent 5,624,679

The Examiner rejects claims 16-18 and 44-46 as allegedly unpatentable over WO 91/12026 in view of Szoka, U.S. Patent 5,077,057 optionally further in view of Sheffield *et al.,* U.S. Patent 4,937,254 further in view of Vournakis, U.S. Patent 5,624,679. As above, the Examiner says that combining chemotherapeutic and anti-estrogens with the agents for anti-adhesion as taught by Vournakis would have been obvious.

The teachings of these references, when combined, do not teach or suggest a composition as described in the method of claim 6 as explained above. As claims 16-18 and 44-46 depend on claim 6, these claims are also patentable.

5. The presently claimed compositions provide unexpectedly superior results.

It is a fundamental principle of the patent law that subject matter that might otherwise be unpatentable may be rendered patentable when it provides unexpectedly superior properties or results. As noted in the foregoing explanations, ***the Examiner has failed to set forth a proper prima facie case of obviousness because the references, even when combined, do not teach the compositions described in the presently claimed methods.*** Nonetheless, even if, *assuming arguendo*, the Examiner had set forth a proper *prima facie* case of obviousness, Applicant submits that the presently claimed methods are still patentable. Applicant presents further data to more clearly show the ratios of the compositions described by the presently claimed methods, ratios neither taught nor suggested by the prior art, are important to provide improved surface tension lowering activity (which is correlated with decreased adhesion formation).

Applicant respectfully refers to the Declaration of Duncan Lawrence pursuant to 37 C.F.R. §1.132 submitted herewith. The data therein illustrate an example of a phospholipid vesicle - LMS-171 - comprising 100% phosphatidylcholine (this illustrates the effect observed if the phospholipid suspension described by WO91/12026 is formulated in the same way as the present invention), and a phospholipid vesicle – LMS-524 – comprising the phospholipids of the compositions described in the presently claimed methods in the ratios as described, but without cholesterol (this illustrates the effect observed if the phospholipids described by WO91/12026) formulated in the same way as the present invention and provided at the same ratios of the present invention (as noted above, the claimed ratio is not taught or suggested by WO91/12026). LMS-261 and LMS-351 illustrate the effect observed when cholesterol is added to a composition mostly comprising phosphatidylcholine and a percentage of cholesterol higher than the compositions of the presently claimed methods. LMS-621 illustrates the effect observed when cholesterol is added to a composition containing the phospholipids of the compositions of the presently claimed methods but containing cholesterol at a percentage significantly more than the compositions of the presently claimed methods.

Applicant again respectfully refers to the Declaration of Duncan Lawrence pursuant to 37 C.F.R. §1.132 submitted herewith. The Declarant declares under oath and penalty of perjury that the lipid compositions LMS-171, LMS-261, LMS-351, LMS-611, LMS-524 and LMS 621 were prepared as described at paragraph [0147] of the present patent application. (*See*, Lawrence Declaration, paragraph 2) Figure 1 and Table 1 provided in Appendix A report the surface tension of different lipid compositions. These data show the surface tension of the compositions according to the presently claimed methods to be significantly lower than that of other lipid compositions. In view of these results, the compositions of the presently claimed methods are predicted to be more effective in preventing adhesions. (*See*, Lawrence Declaration, paragraph 3) Figure 2 provides an electron micrograph image of a composition according to the presently claimed methods showing this takes the form of multi-lamellar vesicles. (*See*, Lawrence Declaration, paragraph 4) The ratio of cholesterol in the composition has been found to be critical for activity. When the ratio of cholesterol is increased (e.g. to 36% as in LMS-621) or removed (e.g. to 0% as in LMS-542) the composition is not as effective in lowering surface tension. Cholesterol present in a ratio of 4-12% of the composition is considered to produce the optimum vesicle structure with the necessary flexibility, deformability and permeability for anti-adhesive activity. (*See*, Lawrence Declaration, paragraph 5)

As indicated by the measured surface tension in the far right hand column of Table 1 and as clearly shown in the graph of Figure 1, ***none of the illustrated compositions lower the surface tension as significantly as LMS-611, a composition according to the presently claimed methods***. Based on these further data, the claimed methods using the compositions described are patentable. As is clear from these further data, a ratio of phospholipids as recited in the present claims and 4-12% cholesterol as recited in the present claims is important to provide improved surfactant activity. Such is an unexpectedly superior property and result of the presently claimed methods.

The ratio of cholesterol taught by Szoka and Sheffield *et al.* (a 1:1 or 1:2 ratio) to form vesicles for the delivery of compounds which exhibit poor aqueous solubility would be rigid, have poor deformability and have low permeability. Such vesicles are not optimal for the presently claimed methods. Neither Szoka, nor Sheffield *et al.*, nor WO91/01206 teach or suggest a ratio of cholesterol that would advantageously provide flexible, deformable and permeable vesicles, for the prevention of adhesions, as provided in the presently claimed methods.

Rejection under the judicially created doctrine of obviousness type double patenting

The Examiner rejects claims 1-4, 20-21, 35-38, 40-46 and 56-59 as allegedly provisionally unpatentable as obvious over copending claims 1-15 of United States Serial No. 10/827,172. Applicant again reiterates a willingness to file a Terminal Disclaimer upon notification of allowable subject matter.

FEES

No additional fees are believed necessary in connection with the present submission; however, should this be in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overage.

CONCLUSION

It is believed that all of the claims are patentable and early notification as such is earnestly solicited. If any issues may be resolved by way of telephone, the Examiner is invited to call the undersigned at the telephone number indicated below.

Respectfully submitted,

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